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The synthesis of C3 and C10 analogs of Cryptophycin A and Arenastatin A is currently under way. The C3 stereocenter can be inverted by substituting (*R*)-leucic acid with (*S*)-leucic acid to determine whether the R configuration at C3 is required for bioactivity. To date, the southern half of C3 epi-Arenastatin A has been prepared. The C10 analogs will be prepared to determine the necessity of the aromatic C4' oxygen on the C10 side chain. Chlorinated phenylalanine C10 analogs are being prepared by chlorination of (*R*)-tyrosine, followed by deoxygenation. The synthesis of the phenylalanines necessary for the synthesis of the C10 analogs has been carried out and is currently being optimized. The synthesis and scale up of the Cryptophycin A and Arenastatin A C10 tyrosine building blocks has been completed. Studies for the stereoselective epoxidation in the final epoxidation to form Arenastatin A and Cryptophycin A, are being examined. Thus far, *in situ* chiral dioxiranes and a sterically hindered peracid have been tested.

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Suzanne B Buck 4/13/99

PI - Signature Date

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Introduction

Cryptophycins are antimitotic, cyanobacterial metabolites isolated from the blue-green algae *Nostoc* sp. GSV 224[1,2] and ATCC 53789.[3] Cryptophycin A (**1**), is the most abundant cytotoxin of the cryptophycins.[4] Its structure was determined by Moore and coworkers in 1995 (Figure 1).[5] A synthetic analog, Cryptophycin-52 (**2**), containing a *gem*-dimethyl group at C6 is currently in clinical trials (Figure 1). A close structural relative of the cryptophycins, Arenastatin A (**3**), was isolated from the Okinawan marine sponge *Dysidea arenaria*.[6] Arenastatin A differs from Cryptophycin A in that it lacks both the chlorine on the aryl ring at C10 and the methyl group at C6.[6]

Microtubules are dynamic components and are essential to cellular life. They are involved with many cell processes such as cell growth, division, locomotion, and intracellular transport. Within the past year, it was discovered that Cryptophycin A and Cryptophycin-52 interact with tubulin to stabilize the dynamics at picomolar concentrations, without altering the microtubule content or organization.[7,8] Earlier, it was known that micromolar concentrations of cryptophycin inhibited tubulin polymerization[1,9] by targeting tubulin, altering the microtubule/tubulin equilibrium, and causing it to depolymerize and form aggregates within cells.[9,10] More recent studies have indicated that the mechanism of action may involve the interaction of cryptophycin at the microtubule ends.[7,8] For Cryptophycin A, the ratio of cryptophycin concentration to the concentration of tubulin was calculated to be approximately 1:400.[8] Cryptophycin-52 is even more potent, having a ratio of approximately 1:2,500,[7] making it the most potent stabilizer of microtubulin dynamics currently known.

In vitro testing demonstrated that the IC_{50} for Cryptophycin A is 0.016 nM in the MCF-7 breast carcinoma cell line.[2] Cryptophycin-52 was found to have a similar IC_{50} of 0.037 nM in the MCF-7 cell line.[11] Similar to Cryptophycin A, Cryptophycin-52 also retains its activity against multidrug resistant phenotypes.[11] The C6 *gem*-dimethyl group effectively decreases the rate of hydrolysis of the ester bond *in vivo*, thereby affording a longer half-life of the compound. Cryptophycin-52 is currently undergoing clinical evaluation for cancer chemotherapy because of its wide range of activity against a variety of tumor models, coupled with its increased stability and its similar potency to Cryptophycin A.[7]

To date, no extensive structure-activity relationship (SAR) studies have been published regarding the C10 side chain, although a variety of analogs of the C16 side chain have been synthesized[12] along with numerous variations on the C5 to N8, β-alanine portion of the molecule.[13]

Al-awar *et al.* synthesized a wide variety of C16 analogs that have helped provide insight about the SAR of the aryl ring.[12] Al-awar and coworkers have shown that if the aryl ring is substituted in the *para* position with an electron donating group, the activity decreased.[12] This is most likely due to the destabilization of the epoxide by the electron donation of the substituent. When the aryl ring was connected with an amino group using a one carbon linker, the *in vivo* potency greatly increased, yet the therapeutic window was unfortunately greatly decreased due to a decreased maximum tolerated dose.[12] When the C16 phenyl ring was replaced with a thiazole ring, the analog had greatly diminished activity.[12]

Shih *et al.* found that if they introduced a substituent at the C7 position or substituted various α-L-amino acids for the C5 to N8, β-amino acid region, the activity decreased.[13] The only C7 substituted analogs that had better activity than Cryptophycin-52 and Cryptophycin A were C7 substituted chlorohydrin derivatives.

Body

Toward the Synthesis of Arenastatin A and Cryptophycin A

The retrosynthetic analysis of Cryptophycin A is shown in Figure 2. The synthesis and scale up of the backbone **4b** (Scheme 1),[14] and the C10 tyrosine building blocks **15** and **19** (for Arenastatin A and Cryptophycin A, Schemes 2 and 3, respectively) have been completed. *(S)*-Leucic acid (**5**) is commercially available, and the β-alanine moiety **6a** can be derived from a substituted β-lactam **6b**.

The synthesis of **4b** [14,15] was accomplished in 11 steps from di-ketoester **8** (Scheme 1). The two stereocenters were set in the first two steps using an enantioselective Noyori hydrogenation, followed by a Frater alkylation. Starting with 8.0 g of **8** afforded approximately 0.32 g of backbone **4b**, a 3% yield overall.

Synthesis of the Arenastatin A Building Block

The synthesis of the Arenastatin A C10 building block **15** begins with the methylation of *N*-Boc-(*R*)-tyrosine methyl ester using dimethyl sulfate (Scheme 2). After methylation, ester **14** was hydrolyzed using 1N sodium hydroxide in 1,4-dioxane. These two steps afford the C10 building block of Arenastatin A in 99% overall yield from the *N*-Boc-(*R*)-tyrosine methyl ester.

Synthesis of C10 Cryptophycin A Building Block

The synthesis of the Cryptophycin A C10 building block **19** begins with the chlorination of (*R*)-tyrosine methyl ester hydrochloride using sulfuryl chloride in acetic acid (Scheme 3). After chlorination, the hydrochloride salt **16** was Boc-protected using di-*tert*-butyl dicarbonate. The phenol was then methylated using dimethyl sulfate, and ester **18** was hydrolyzed using 1N lithium hydroxide in 1,4-dioxane. These four steps afforded the C10 side chain in 82% overall yield from (*R*)-tyrosine methyl ester hydrochloride.

Synthesis of Analogs

Modification of the C3 Center

Moore *et al.* tested cryptophycin analogs isolated from *Nostoc* sp. GSV 224.[5] Their data suggested that the binding site of the cryptophycins contains a hydrophobic pocket, where the C3 isobutyl group interacts favorably. To date, inversion of the C3 center has not be done. I propose that by keeping the isobutyl group unchanged and inverting the stereochemistry at C3, information on the orientation of the hydrophobic binding site will be gained.

The synthesis of the C3 epimer of Arenastatin A is currently underway, substituting (*R*)-leucic acid for (*S*)-leucic acid. Although (*S*)-leucic acid is commercially available, (*R*)-leucic acid is not. Therefore, it was necessary to convert (*R*)-leucine to (*R*)-leucic acid (**20**) using a known diazotization procedure (Scheme 4).[16] (*R*)-Leucic acid (**20**) was protected using allyl bromide and then coupled with *N*-Boc-protected β-alanine, to afford compound **22**. Compound **22** was then deprotected using trifluoroacetic acid and subsequently coupled to methyl tyrosine **15**. This afforded the protected "southern half" of C3 epi-Arenastatin A **23**. The allyl group was cleaved using tetrakis(triphenylphosphine)-palladium(0), to afford **24**.

Compound **24** will be activated using the Yamaguchi reagent, 2,4,6-trichlorobenzoyl chloride, and then coupled to the deprotected backbone **4b** (Scheme 5). The *N*-Boc group and the *tert*-butyl ester will be cleaved from intermediate **25** using trifluoroacetic acid. The trifluoroacetic acid salt will then be used directly, without purification, and joined to the acid moiety of the backbone using *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU) as the coupling reagent. This will complete the macrolide structure. Finally, an

epoxidation using *m*-chloroperbenzoic acid (*m*-CPBA) will be done to yield a mixture of the α:β epoxides of C3 epi-Arenastatin A (**27**).

Modification of the C10 Sidechain

The SAR studies done by Moore *et al.* have shown that removal of the C10 aryl C3' chlorine or the C4'-*O*-methyl group causes the loss of *in vivo* activity[5] (see Figure 2 for numbering system). Because removal of the chlorine and the methyl group decrease the lipophilicity of Cryptophycin A, this implies that lipophilicity may be very important in the activity of the molecule.

Isolated aryl C3',5'-dichloro, C4'-*O*-methyl substituted and aryl C3',5'-dichloro, C4'-hydroxy compounds also had decreased activity *in vitro*.[5] This could be due to the increased steric bulk of the aryl ring. Therefore, in order to more thoroughly test this hypothesis, I will synthesize two chlorinated phenylalanine analogs.

Synthesis of the chlorinated analogs begins with the chlorination of (*R*)-tyrosine methyl ester hydrochloride (**28**), using sulfuryl chloride to afford either the mono- or dichlorinated product (Scheme 6). Depending on the number of equivalents of sulfuryl chloride used, either the mono- or dichlorinated product can be obtained. The chlorinated compounds were then *N*-Boc protected, and converted to the corresponding mono- and dichlorinated triflates (**31** and **32**, respectively) using triflic anhydride. Next, the triflates **31** and **32**, were subjected to a palladium catalyzed deoxygenation using palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) to afford the deoxygenated compounds **33** and **34**, (46% and 28%, respectively, unoptimized).[17] The methyl esters will be hydrolyzed using 1N sodium hydroxide, forming the mono- and dichlorinated acids (**35** and **36**, respectively). These acids will then be substituted for the (*R*)-tyrosine compound **15** in the "southern half" synthesis (Scheme 4).

When synthesized, the aryl C3'-chlorophenylalanine analog, will be tested for its *in vitro* activity. If lipophilicity does play an important role in the activity of the molecule, the elimination of the aryl C4'-methoxy group, yielding a slightly more lipophilic analog, should have *in vitro* activity comparable to Cryptophycin A. To confirm the outcome of this experiment, the highly lipophilic aryl C3',5'-dichloro phenylalanine analog will also be prepared and tested for *in vitro* activity. There are four possible outcomes that have to be considered regarding the activity of the two analogs.

The first possibility, that neither of these analogs exhibits comparable activity to Cryptophycin A, would suggest that the aryl C4'-methoxy substituent, or a comparable moiety, is necessary to interact with a lipophilic binding site.

A second possibility, if the monochlorinated analog shows activity, and the dichlorinated compound has decreased activity, would strongly suggest that the binding pocket of the aryl ring only has room for a single specific lipophilic interaction on one side. By introducing the second chlorine, the first site can no longer be accommodated due to the inability of the second chlorine to fit into the binding pocket.

A third possibility, that the dichloro analog would exhibit activity while the monochloro compound had reduced activity, would suggest that the binding sight can accommodate the steric requirements for substitution at the aryl C3' and C5' sites, and that the monochlorinated compound, had reduced activity due to decreased binding interaction.

The fourth, and final possibility, that both analogs exhibit activity, would suggest that the C10 aryl, C4' substitution is not necessary as long as the lipophilicity of the aryl ring is comparable to Cryptophycin A. Again, this would also suggest that the binding site could accommodate steric demands of the C3',5'-disubstituted compounds.

Alternative Deoxygenation Procedures to Chlorophenylalanines

Currently, alternative methods of deoxygenation are being pursued to optimize the reaction conditions. To date, seven different deoxygenation reactions have been carried out, and the best

conditions provide a modest 46% yield of the monochlorinated product **33**, and a 28% yield of dichlorinated product **34** (Table 1). To determine the best deoxygenation conditions, the dichlorophenylalanine compound was chosen because it is the more difficult compound to deoxygenate.

Initially, the deoxygenation of **32** was attempted via entries 1 ($Pd(OAc)_2$, PPh_3, TEA, HCO_2H) and 2 (TEA, Pd/C, H_2) but both conditions failed; entry 1 provided only the phenol **30**, and entry 2 yielded a trace amount of product **34**, along with phenol **30**. I then substituted a ferrocene ligand for the triphenylphosine, and was able to deoxygenate (entry 3, $Pd(OAc)_2$, DPPF TEA, HCO_2H). Attempts to improve the yield by altering the base (entry 4, *n*-butylamine for TEA), or catalyst (entry 5, $Pd(PPh_3)Cl_2$ for DPPF) used in entry 3, were not seen. These modifications of entry 3 conditions yielded only phenol **30**.

Alternative routes of deoxygenation not utilizing a triflate were examined. Tosylate **37** was prepared (Scheme 7),[18] and subjected to the conditions of entry 6[18] (Table 1). This again provided phenol **30** as the major product. Similar results were obtained when the *n*-$C_4F_9O_2S$-derivative of **30**, entry 7, was prepared[19] (Scheme 8) and subjected to the conditions of the successful entry 3.

Further studies will examine the altering the conditions and/or reagent equivalents to increase the yield.

Epoxidation Studies

Epoxidation is the final step in the synthesis of the epoxide-containing arenastatin and cryptophycin compounds. Although numerous syntheses of both the arenastatins and cryptophycins have been published,[1,6,20-23] the epoxidation step has always[24] been done using *m*-CPBA or dimethyldioxirane. This is of significance because the two diastereomers formed, at best in a 2:1 ratio of β:α epoxides, cannot generally be separated by column chromatography. It is necessary to use high performance liquid chromatography to separate them. This is a time consuming procedure and is limited by the amount of compound that can be loaded onto a given column. Consequently, we have been testing alternative methods of epoxidation in the final step of the synthesis.

Because of the number of steps required to synthesize desepoxy-Arenastatin A (**43**, Figure 3) which is epoxidized to form Arenastatin A (**3**, Figure 1), the commerically available β-trans-methyl styrene was initially used as a model system. Figure 4 shows the different reagents used to epoxidize β-trans-methyl styrene and intermediate **43**.

The use of the *in situ* chiral dioxirane **39** has recently been reported by Wang *et al.*[25] The dioxirane is generated by adding a solution of Oxone® in buffer to a prepared solution of the ketone of **39**, the olefin to be epoxidized, and phase transfer catalyst, in a buffer solution. After forming in the aqueous layer, the dioxirane migrates to the organic phase and interacts with the lipophilic olefin. We hypothesized that the chiral dioxirane would interact with the desepoxy-Arenastatin A (**43**) and stereospecifically deliver the oxygen to the double bond, thereby substantially increasing the ratio of the β:α epoxides.

The use of the hindered *in situ* dioxiranes **40** and **41** is also being pursued in the hopes that the steric requirements demanded by the cryptophycin and arenastatin analogs will more strongly favor the epoxidation of the least hindered face. Using *m*-CPBA, the ratio of α:β epoxides is 1:2, in favor of the β-epoxidation to the less sterically hindered side. Dioxiranes **40** and **41** are easily generated *in situ,* using the same procedure as was used to form dioxirane **39**.

The bulky peroxypivalic acid **42** was also prepared to test the hypothesis that if we increased the steric demands of the epoxidant, that the stereospecificity of the reaction would increase. Peroxypivalic acid **42** was obtained by adding 50% hydrogen peroxide to a solution of peroxypivalic acid in sulfuric acid.[26]

All of the epoxidations of β-trans-methyl styrene were successful using *in situ* dioxiranes, **39**, **40** and **41**, and peroxypivalic acid (**42**).

Epoxidation of desepoxy-Arenastatin A (43)

To date we have tried to epoxidize intermediate **43** using the chiral dioxiranes **39** and **40** that were generated *in situ*. Dioxirane **41**, was used to epoxidize β-trans-methyl styrene but isolation of the reaction products were problematic. Therefore, the use of this reagent to epoxidize the double bond of **43** was not attempted.

Neither of the dioxiranes **39** and **40** epoxidized intermediate **43**. The problematic factor in these procedures seems to be related to the solubility of the desepoxy-Arenastatin A in the biphasic solution necessary to generate the dioxiranes *in situ*. After adding the aqueous phase, the desepoxy-Arenastatin A (**43**) precipitated. Epoxidation with peroxypivalic acid (**42**) was attempted. Partial conversion to the epoxide was seen, but attempts to force the reaction to completion failed.

Future studies will look at isolating the dioxiranes and then using them to epoxidize intermediate **43** in non-aqueous conditions. Other bulky peracids are currently being considered as possible oxidants.

Conclusion

There are five major areas that I have planned to addressed in my research project. (1) Cyclizing the cryptophycin macrocycle, utilizing a novel lactonization technique involving a highly activated β-lactam. (2) Synthesizing the arenastatin analog with the inverted C3 center, using (*R*)-leucic acid instead of the biologically common (*S*)-leucic acid. (3) Modifiying the β-lactam to introduce both the ethyl and *gem*-dimethyl groups at C6, and to invert the stereochemistry at C6. (4) Modifying the aryl moiety in the side chain of C16. (5) Modifying the aryl ring at C10 by substituting various phenylalanine and tyrosine derivatives during the synthesis. In addition to the original goals, I have synthesized the two different tyrosine building blocks necessary for the synthesis of Cryptophycin A and Arenastatin A. Also, I have tried to find a stereoselective ways to carry out the final epoxidation step to afford a higher ratio of β:α epoxides.

The first area of my research project, cyclizing the macrolide via a novel lactonization technique, has not been performed to date.

The synthesis of the arenastatin analogs containing the (*R*)-leucic acid, the second area of my project, is currently under way (Scheme 5). To date, the southern half of the molecule, intermediate **24**, has been synthesized, and is in the process of being scaled up. Two analogs will be synthesized with the inverted C3 center. One analog will contain the (*R*)-tyrosine side chain that is present in Cryptophycin A, and the second analog will contain the tyrosine side chain present in Arenastatin A.

The third, and fourth areas of my project have yet to be initiated.

The fifth area of my research, is in progress (Scheme 6). The synthesis of the deoxygenated C10 tyrosine building blocks **35** and **36** is near completion. Currently, ways to optimize the deoxygenation step are being pursued.

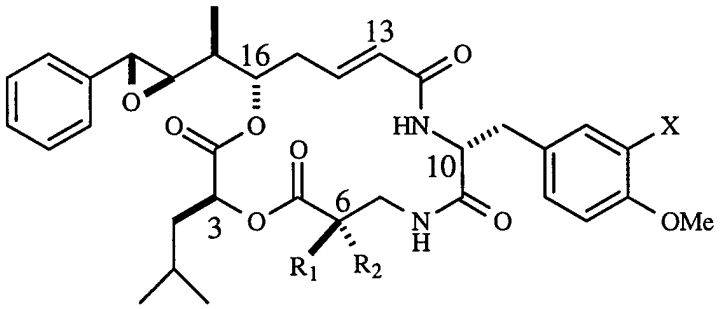
The synthesis of the tyrosine building blocks **15** and **19**, necessary for the synthesis of Arenastatin A and Cryptophycin A, respectively, has been completed. The epoxidation studies are still under investigation. The solubility problem will be addressed, and if necessary, alternative epoxidation methods will be explored.

Addena A:
Acronyms and Symbol Definition

AcOH - acetic acid
ATCC - American type Culture Collection
BOC_2O-di-*tert*-butyl dicarbonate
m-CPBA - *m*-chloroperoxybenzoic acid
DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC - 1,3-dicyclohexylcarbodiimide
DIBALH -diisobutylalumnium hydride
DIEA - diisopropyl ethylamine
DMAP - 4-dimethylamino pyridine
DMF - *N*-dimethylformamide
DPPF - 1,1'-bis(diphenylphosphino)ferrocene (DPPF
HBTU - *O*-benzotriazol-1-yl- *N,N,N',N'*-tetramethyluronium hexafluorophosphate
HF -hydrogen fluoride
HOBT - 1-hydroxybenzotriazole hydrate
LDA - lithium diisopropyl amide
MeI - methyl iodide
NMO - 4-morpholine *N*-oxide
Oxone® - potassium peroxymonosulfate
Pd/C - palladium on carbon
$Pd/(PPh_3)Cl_2$ - bis-(triphenylphosphine)-palladium(II)chloride
$Pd(PPh_3)_4$ - tetrakis(triphenylphosphine)-palladium(0)
PPh_3 - triphenyl phosphine
RT - room temperature
SAR - structure-activity relationship
TBSCl - *tert*-butyldimethylsilyl chloride
TEA - triethylamine
Tf_2O - triflic anhydride
THF - tetrahydrofuran
TPAP - tetrapropylammonium perruthenate
TsCl - *p*-toluenesulfonyl chloride

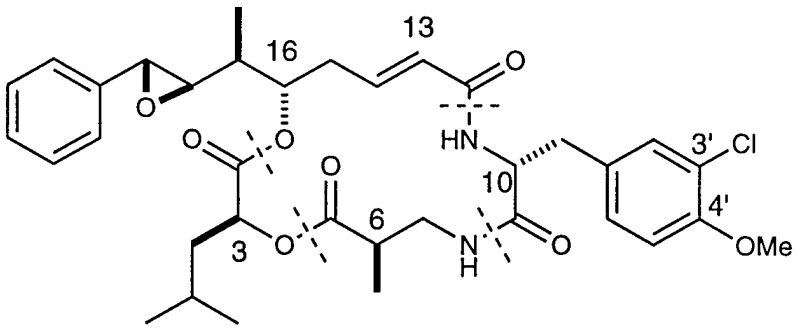
Addena B:
Figures, Schemes and Table

Figure 1. Structures of Cryptophycin A, Cryptophycin-52 and Arenastatin A.

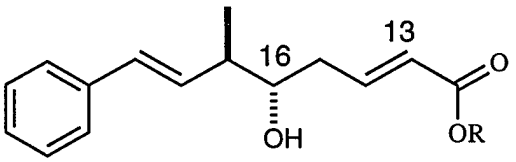


Cryptophycin A (**1**) X = Cl; $R_1 = CH_3$, R_2 = H
Cryptophycin-52 (**2**) X = Cl; R_1, $R_2 = CH_3$
Arenastatin A (**3**) X = H, R_1, R_2, = H

Figure 2. Retrosynthetic analysis of Cryptophycin A.

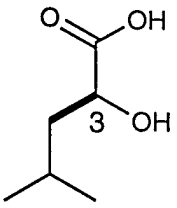


Cryptophycin A (**1**)



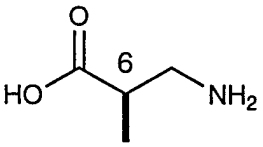
Backbone

4a, R = H
4b, R = *t*-Bu



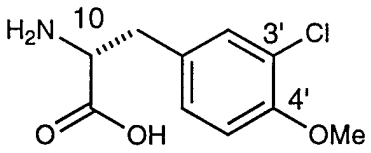
5

(*S*)-Leucic Acid



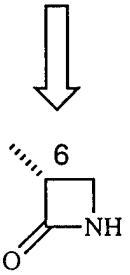
6a

β-Alanine Moiety



7

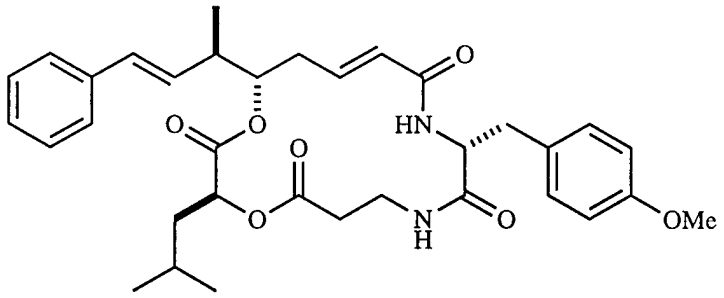
(*R*)-Tyrosine Derivative



6b

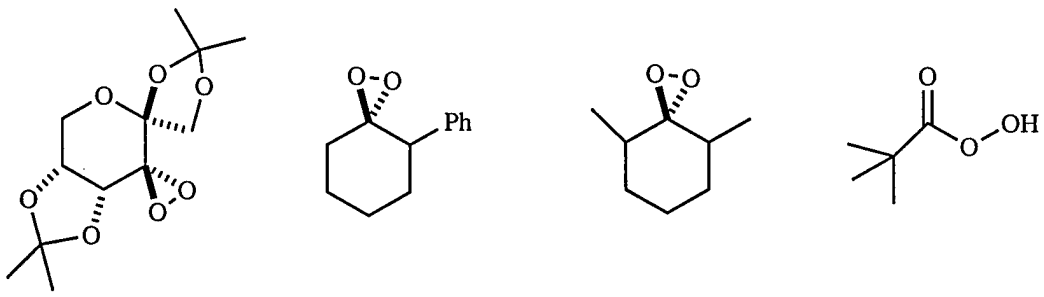
β-Lactam Moiety

Figure 3. Structure of desepoxy-Arenastatin A (**43**).



43

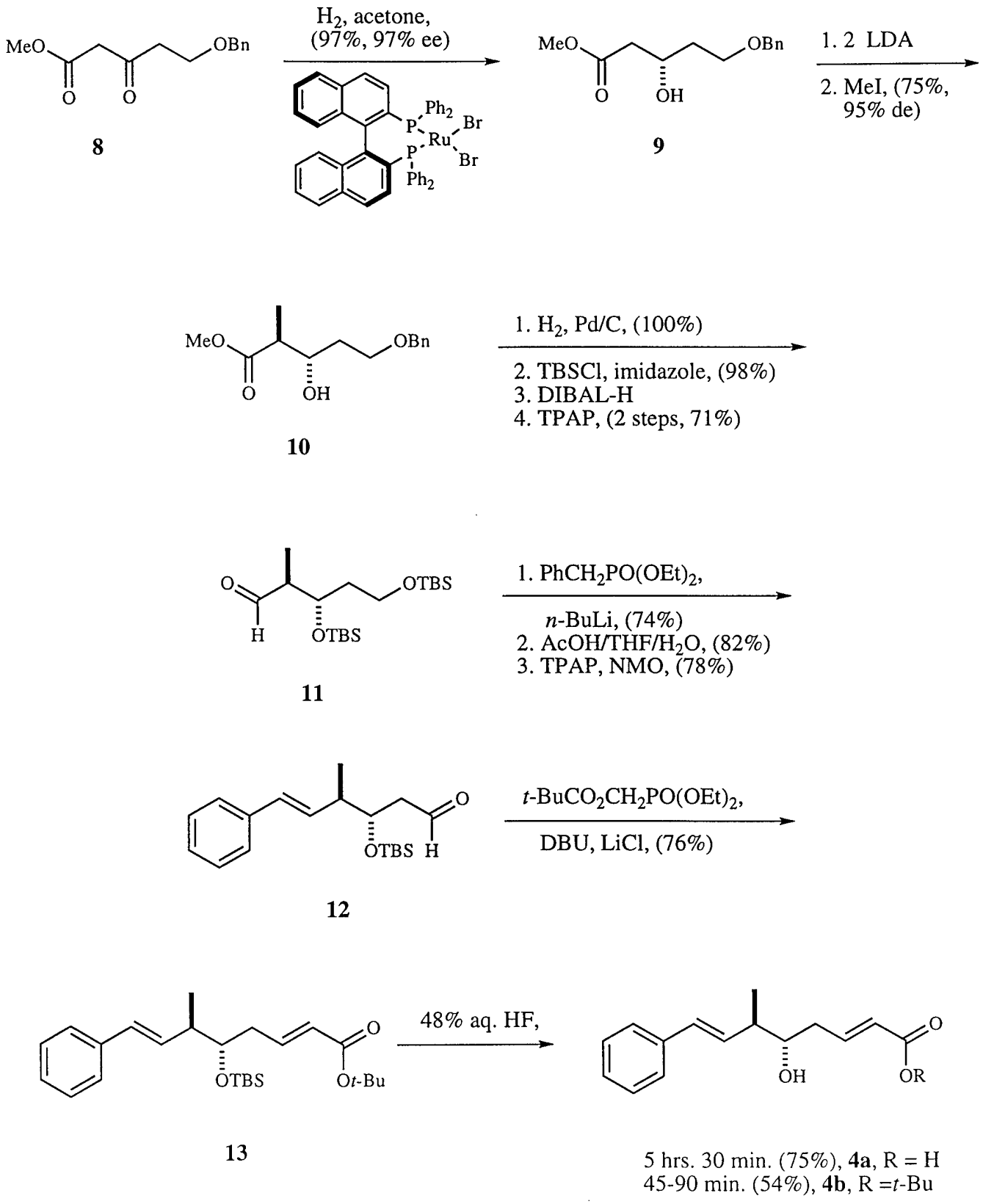
Figure 4. Epoxidation reagents.



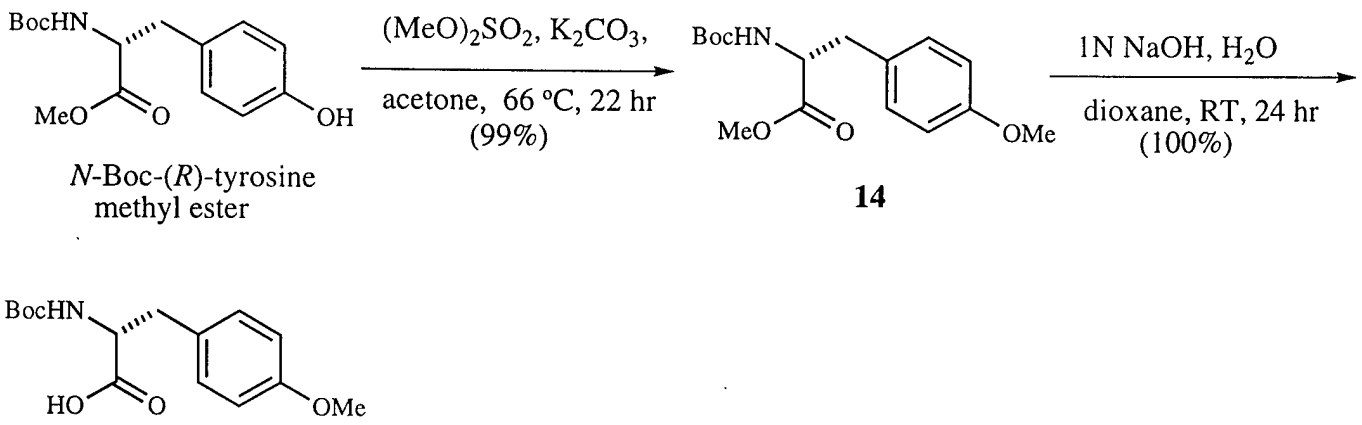
39 **40** **41** **42**

in situ dioxiranes

Scheme 1.


MeO
OBn
O
O
8
H2, acetone,
(97%, 97% ee)
Ph2
P
Ru
Br
Br
P
Ph2
MeO
OBn
O
OH
9
1. 2 LDA
2. MeI, (75%,
95% de)
MeO
OBn
O
OH
10
1. H2, Pd/C, (100%)
2. TBSCl, imidazole, (98%)
3. DIBAL-H
4. TPAP, (2 steps, 71%)
O
OTBS
H
OTBS
11
1. PhCH2PO(OEt)2,
n-BuLi, (74%)
2. AcOH/THF/H2O, (82%)
3. TPAP, NMO, (78%)
O
OTBS H
12
t-BuCO2CH2PO(OEt)2,
DBU, LiCl, (76%)
OTBS
Ot-Bu
O
13
48% aq. HF,
OH
OR
O
5 hrs. 30 min. (75%), 4a, R = H
45-90 min. (54%), 4b, R =t-Bu

Scheme 2.



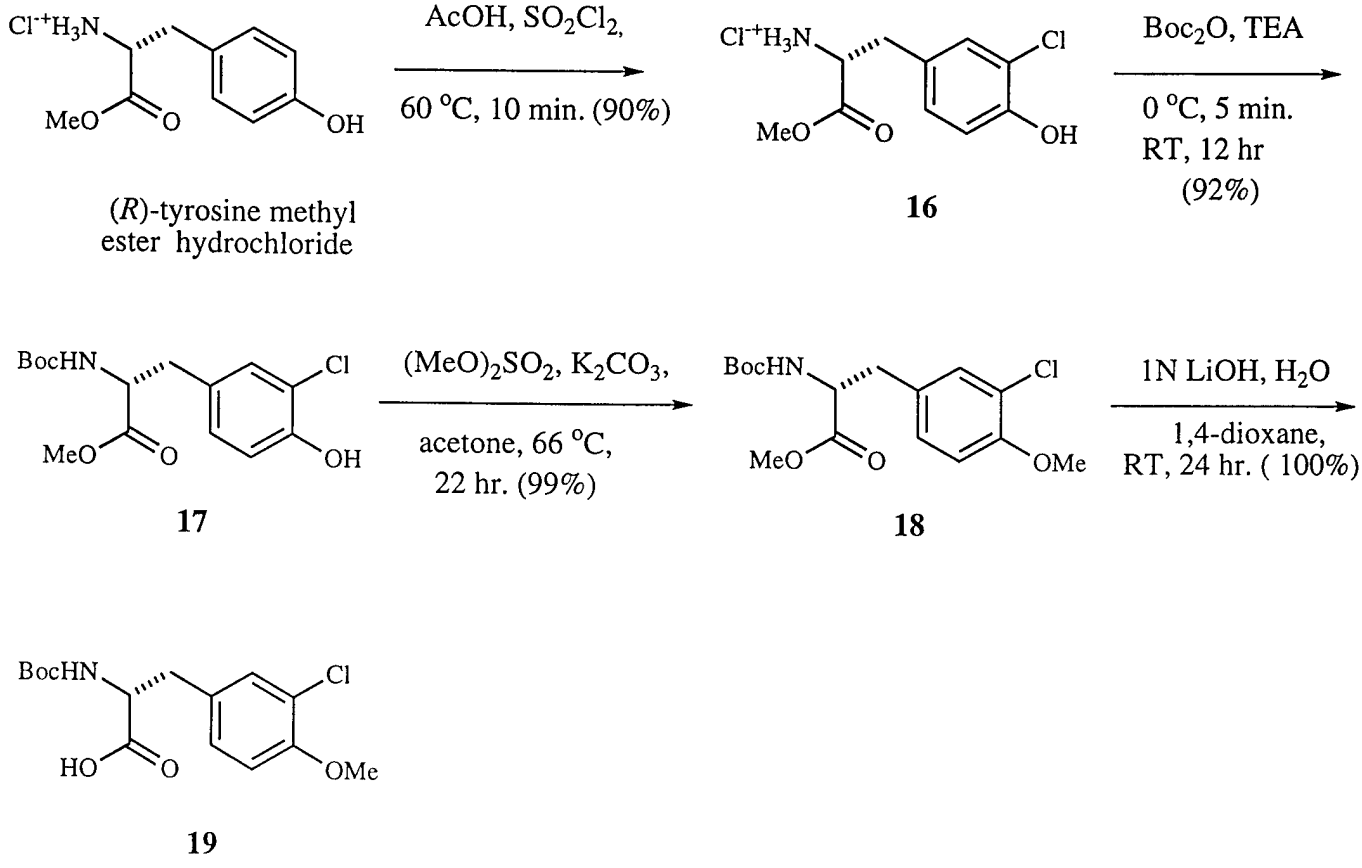
N-Boc-(*R*)-tyrosine methyl ester

14

15

C10 Arenastatin A building block

Scheme 3.



(*R*)-tyrosine methyl ester hydrochloride

16

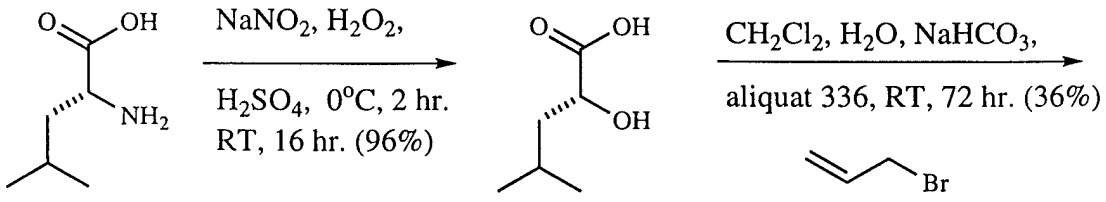
17

18

19

C10 Cryptophycin A building block

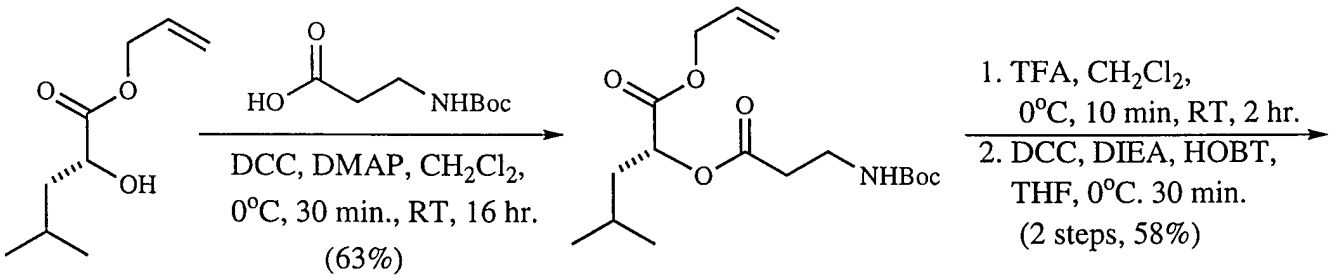
Scheme 4.



(*R*)-leucine

20

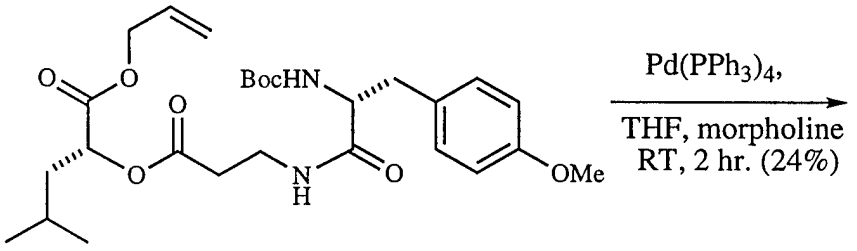
(*R*)-leucic acid



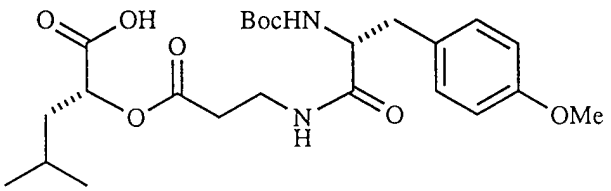
21

22

15



23



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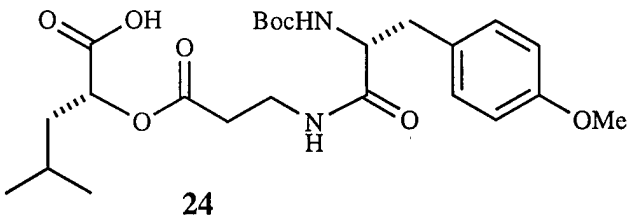
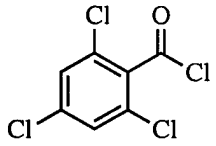
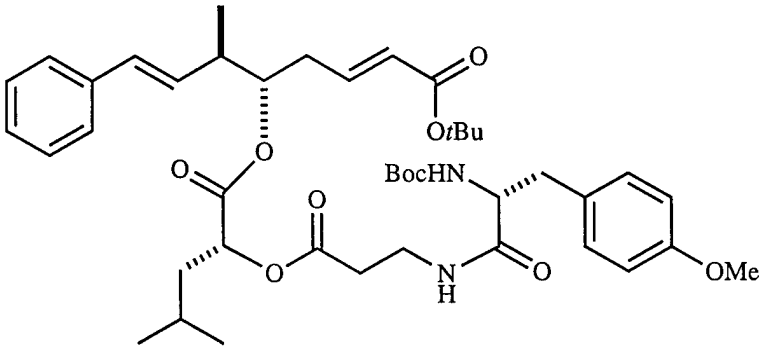
Scheme 5.



24

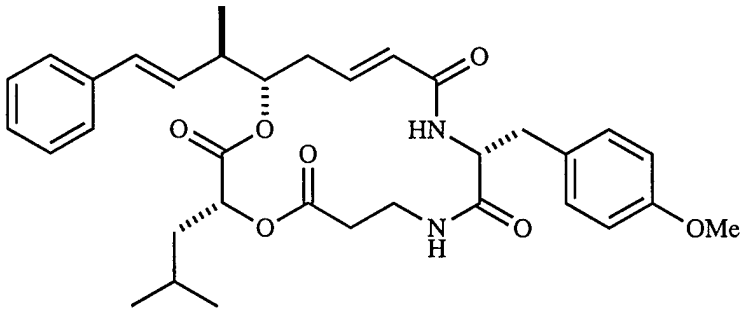
DIEA, DMAP, THF, **4b**





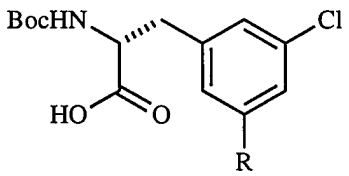
25

1. TFA, CH_2Cl_2
2. HBTU, DIEA, CH_3CN

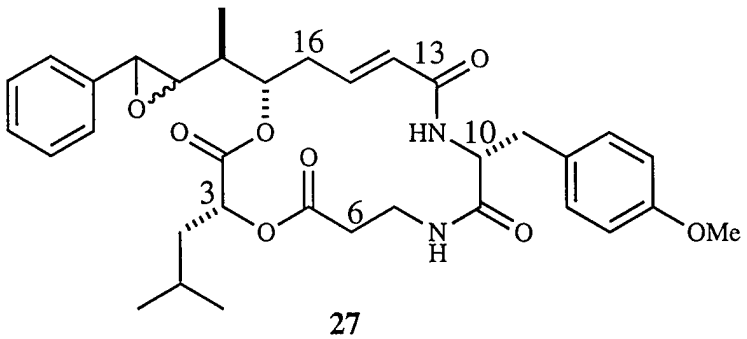


26

m-CPBA, CH_2Cl_2



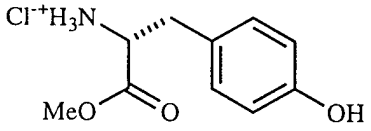
35, R = H
36, R = Cl



27

C3 epi-Arenastatin A
mixture of epoxides

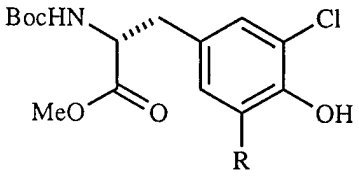
Scheme 6.



28
(*R*)-tyrosine methyl ester hydrochloride

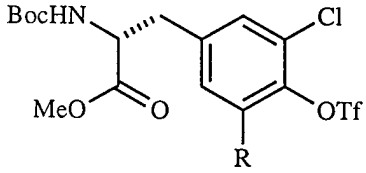
1. SO_2Cl_2, AcOH, Δ, 60 °C, 10 min. (90%)

2. Boc_2O, TEA, CH_2Cl_2 0 °C, 5 min., RT 2 hr. (74%)



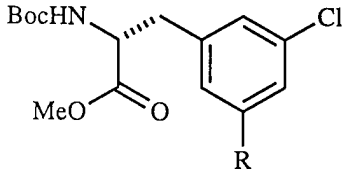
Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min. (100%)

29, R = H, 1.0 equiv. SO_2Cl_2
30, R = Cl, excess SO_2Cl_2



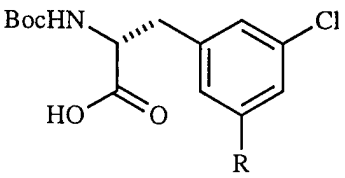
$Pd(OAc)_2$, DPPF, TEA, HCO_2H, DMF 60 °C, 16 hr.

31, R = H, 1.0 equiv. SO_2Cl_2
32, R = Cl, excess SO_2Cl_2



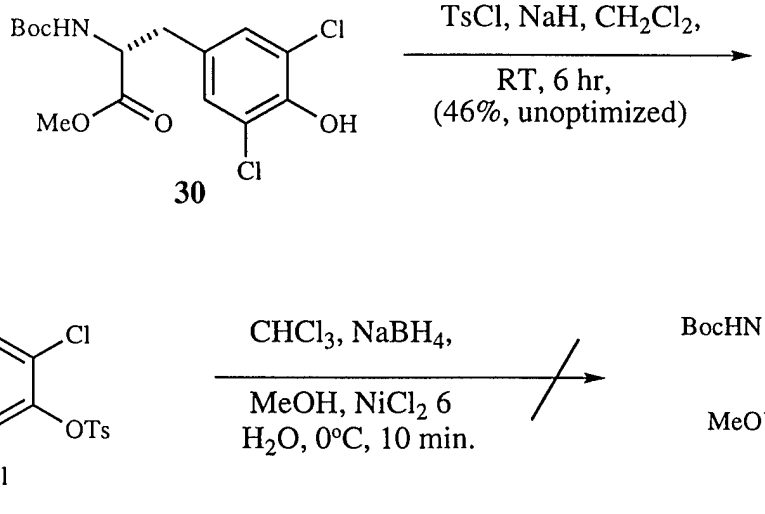
33, R=H, (46%)
34, R=Cl, (28%)

1N NaOH, dioxane



35, R = H
36, R = Cl

Scheme 7.



Scheme 8.

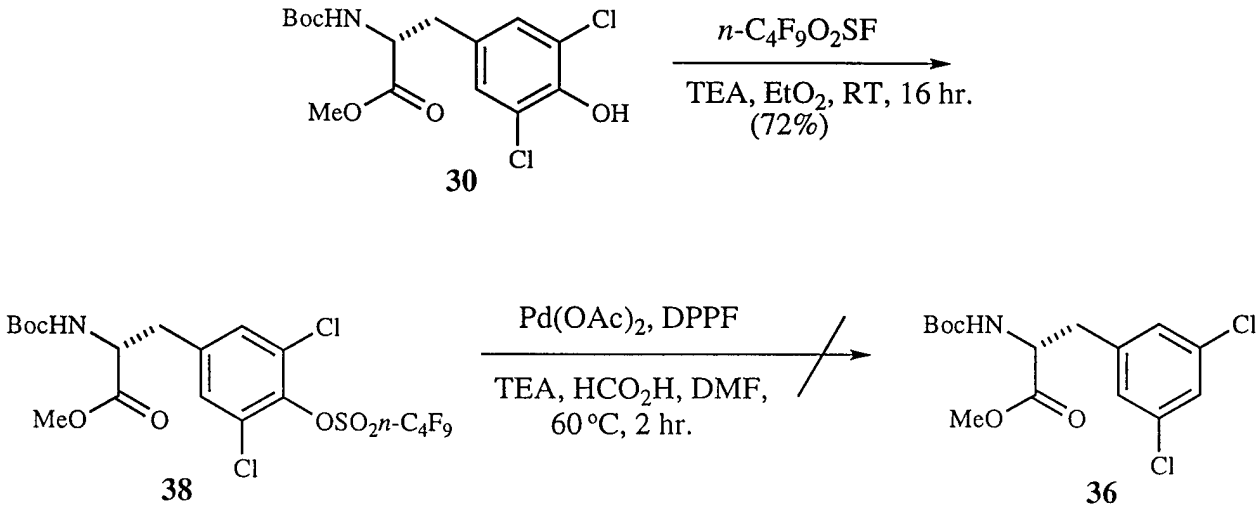
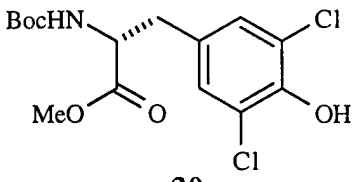
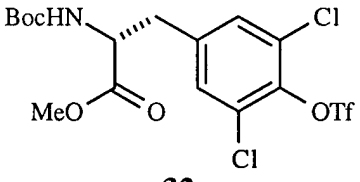


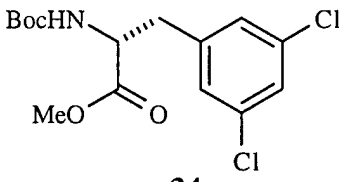
Table 1. Reaction conditions tried to deoxygenate derivatives of **30**.



30



32



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Entry Number	Starting Material	Reagents	Results
1	**32**	$Pd(OAc)_2$, PPh_3, TEA, HCO_2H	phenol **30** recovered
2	**32**	TEA, Pd/C, H_2	trace product **34** seen, phenol **30** recovered
3	**32**	$Pd(OAc)_2$, DPPF TEA, HCO_2H	28% dichloro product **34** obtained
4	**32**	$Pd(OAc)_2$, DPPF, *n*-butylamine, HCO_2H	phenol **30** recovered
5	**32**	$Pd(OAc)_2$, $Pd(PPh_3)Cl_2$, TEA, HCO_2H	phenol **30** recovered
6	tosylate of **30**	$CHCl_3$, $NaBH_4$, MeOH, $NiCl_2$	trace product **34** seen, phenol **30** recovered
7	*n*-$C_4F_9SO_2$- of **30**	$Pd(OAc)_2$, DPPF TEA, HCO_2H	phenol **30** recovered

Addena C:
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